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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,516	07/29/2003	Arnold Horwitz	11307US04 / 200-83.P1.C2	8570

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EXAMINER	
MITRA, RITA	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/629,516	ARNOLD HORWITZ	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Applicants' amendment and response to office action of November 17, 2005, filed on March 16, 2006 is acknowledged. Amendment to the specification is noted. Claims 1, 4-6, 17-19 have been amended. Therefore claims 1-19 are currently under examination.

Response to Amendment and Remarks

Objection to the Specification

1) The objection to the specification is withdrawn in view of amendment to the abstract.

2) The objection to the specification regarding sequence identifier to the embedded sequences is withdrawn in view of an error in citing the page number in the previous office action.

3) Objection to continuing data is withdrawn in view of updating the data.

Claim Rejections - 35 USC § 101-Nonstatutory

Rejection of claims 4 and 5 under 35 USC § 101-Nonstatutory is withdrawn in view of amendment to claims.

Claim Rejections - 35 USC § 112

Rejection of claims 1-19 under 35 USC § 112, second paragraph is withdrawn in view of amendment to the claims.

Rejections - Nonstatutory Double Patenting

Rejection of claims 1-19 under Nonstatutory Double Patenting is withdrawn in view of the approval of the Terminal Disclaimer.

Objection to the Specification

The specification is objected to because the specification describes sequences that are set forth in the "Sequence Listing" and embedded in the text of the specification at pages 6, 8 and

16, however no reference is made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" See 37 C.F.R. § 1.181(d). This objection may be overcome by providing sequence identifier to the embedded sequences.

New Grounds of Rejection

Applicants' amended to claims necessitated the following rejections:

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of **35 U.S.C. 102** that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7-19 are rejected under 35 USC 102(b) as being anticipated by Theofan et al. (US 5,420,019, issued on May 30 1995, priority date claimed February 2, 1993). Theofan et al. teach bacteriocidal /permeability-increasing (BPI) protein products wherein cysteine residue number 132 or 135 is replaced by another amino acid residue preferably an alanine or serine (see abstract, col. 3, lines 43-48), wherein the BPI deletion product has 100% sequence identity to SEQ ID 2, amino acid residue 10-193, wherein a cystine at position 132 is replaced by a serine residue (see sequence alignment result 10, SEQ ID NO: 2, amino acid 10-193, Database: Issued_Patents_AA, , US-08-013-801-2) thus anticipating claims 1-3 of instant application. Further Theofan et al. teach DNA sequences that encode the rBPI protein and protein fragment products including analog products (see abstract, col. 3, lines 65-68), (claims 4, 5,7). Theofan also discloses autonomously replicating DNA plasmid vectors which include DNA encoding the said products and analogs as well as host cells which are stably transformed with said DNA, wherein the host cell is an eukaryotic host cell such as CHO cell, wherein the protein products are prepared by culturing the transformed cells (claims 8-13), see col. 4, lines 2-10 and 26-37; Example 1 and 2. The reference also discloses a pharmaceutical composition comprising the rBPI protein products of the invention in pharmaceutically acceptable diluents, adjuvents and

carriers (claims 14-16), wherein such compositions are useful in the treatment of gram-negative bacterial infection and sequelae thereof (claims 17-19), see col. 4, lines 38-41 and 43-45. Thus Theofan's BPI protein products and analogs are considered for the BPI deletion analog consisting of amino acid residues 10-193 of BPI of SEQ ID NO: 2 of instant application. Accordingly claims 1-19 are anticipated by Theofan et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-19 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Theofan *et al.* (US 5,420,019, May 30 1995) in view of Horwitz et al. (Protein Expression and Purification, vol. 8, pp 28-40, 1996) and further in view of McGregor et al. (US 5,488,034, January 13, 1996).

Theofan et al. is applied as cited in the above rejection. Theofan et al. teach a BPI protein deletion product wherein cysteine residue number 132 or 135 is replaced by another amino acid residue preferably an alanine or serine, wherein the BPI deletion product has 100% sequence identity to amino acid residues 10-193 of SEQ ID 2. Theofan et al. also teach DNA sequences that encode the rBPI protein and fragments and analogs thereof. Theofan also discloses vectors which include DNA encoding the said products and analogs as well as host cells (CHO cell) which are stably transformed with said DNA, wherein the protein products are prepared by culturing the transformed cells (claims 8-13), The reference also discloses a pharmaceutical composition comprising the rBPI protein products of the invention in pharmaceutically acceptable diluents, adjuvents and carriers. This addresses claims 1-5, 7-16. Though Theofan suggests that such compositions are useful in the treatment of gram-negative bacterial infection, however, Theofan does not teach a method of administering a BPI protein product to a subject comprising administering the composition of claims 14, 15 and 16 to said subject.

Horwitz *et al.* teach (i) that the recombinant N-terminal portion of BPI (residues 1-199) retains bactericidal activity (page 28, Introduction, right column, lines 8-14), (ii) a DNA encoding the first 193 amino acids (with or without the desired cysteine mutations)," (page 29, section entitled 'Construction of Expression plasmids containing rBPI193), (iii) a recombinant BPI consisting of residues 1-193 with a C132A mutation (Figure 1, page 30) and (iv) that a C132A modification yields a stable, biologically active, N-terminal BPI fragment (designated $rBPI_{21}$) that is free of dimeric species (page 28, Abstract, right column, lines 6-8). The C132A mutation resulted in a polypeptide that contained no free thiol groups (page 37, right column, lines 6-13) thus preventing cross-linking and dimerization, which teaches that substitution of cysteine with any amino acid not containing sulfur at this position would produce similar biological results as the C132A mutation. Horwitz et al. do not teach the truncation to amino acids 10-193.

Theofan and Horwitz do not teach a method of administering a BPI protein product to a subject comprising administering the composition of claims 14, 15 and 16 to said subject.

McGregor *et al.* teach administration of bactericidal permeability increasing (BPI) protein (see the examples) where the BPI had a mutation at position 132 (see column 5 of the patent), where cysteine is replaced with an alanine. While the McGregor *et al.* patent did not specifically disclose deletion of the first 10 or so amino acids, McGregor *et al.* nevertheless used active fragments of BPI such as $rBPI_{12}$ or any amino-terminal fragment comprising from about the first 193-199 amino terminal amino acid residues of BPI are believed to be susceptible to loss of stability in aqueous solution (column 2). Where McGregor *et al.* also teach using active fragments and that the N-terminus is important to biological function. Theofan et al. and Horwitz *et al.*, have been applied here as indicated above. In addition where McGregor discusses BPI, where the BPI had a mutation at position 132, BPI active fragments and that the N-terminal is important to biological function and is directed to using minimum structural requirements and that deletion of some 12 residues from the N-terminus is without effect on LPS binding, it would have been obvious to one of ordinary skill in the art to have modified the peptides disclosed in the McGregor *et al.* reference by N-terminal truncation for the advantages of using a minimal structure for the active agent. Thus, the process of claims 17-19 of administering a BPI to a subject would have, from the combined cited references have been obvious since the combined references teach administering BPI modified in a manner identical if not similar to that recited in the claims and would have been in an appropriate carrier (see, e.g., McGregor *et al.* at column 3 and example 4, *et seq.*). It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Theofan with the combined teachings of Horwitz and McGregor references to arrive at the invention of claims 17-19. The motivation to combine the teaching of Theofan with the combined teachings of Horwitz and McGregor would come from the desire to administer the recombinant $BPI_{10\text{-}193}$ C132A mutation protein in a formulation that would take advantage of the

bactericidal properties of said protein for administration in an infected subject. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita Mitra whose telephone number is 571-272-0954. The examiner can normally be reached on M-F, 10:00 am-7:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rita Mitra, Ph.D.
May 23, 2006

Jon Weber
Supervisory Patent Examiner